IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kano et al.	Confirmation No.:	7451
Serial No.:	09/823,699	Art Unit:	1633
Filed:	March 30, 2001	Examiner:	Q. Janice Li
Customer No.:	21559		
Title:	AIDS VIRUS VACCINES USING SENDAI VIRUS VECTOR		

DECLARATION OF MAMORU HASEGAWA UNDER 37 C.F.R. § 1.132

I declare:

1. I am an inventor of subject matter that is described and claimed in the above-referenced patent application.

2. I am the President and CEO of DNAVEC Corporation ("DNAVEC"). I hold the degree of Ph.D.

3. I have read and understood the Office Action mailed on June 14, 2007 in connection with the above-referenced patent application.

4. In the Office Action mailed on June 14, 2007, the Office maintained the rejection of claims 2, 4, 5, 7, 9, 11-20, 24, 26, 28-33, 37, 39, 42-45, 62-68; 70, and 73-79 under 35 U.S.C. §103(a) for obviousness and for obviousness-type double patenting. The rejections were based on various combinations of references, including Nagai et al., Yu et al., Hirsch et al., Hanke et al., Flanagan et al., Seth et al., Hurwitz et al., Ourmanov et al., Nakanishi et al., Göttlinger et al., Kast et al., and Boutillon et al. I disagree with these rejections.

5. One skilled in the art would have had no motivation to combine any of the references cited by the Office in order to make, use, or practice the compositions and methods of the claims at the time of filing the present application.

6. The prior use of SeV to express an immunodeficiency viral protein would not have provided a skilled artisan with a reasonable expectation of success in modifying a Vaccinia-based vaccine by substituting SeV for Vaccinia virus. This is so because Vaccinia virus is a DNA virus, whereas SeV is a negative-strand RNA virus. RNA and DNA viruses differ not only in terms of structure, but also in terms of functionality and biosynthesis. For example, when a DNA virus infects host cells, the cells transcribe viral DNA to make mRNA and the host cell translation machinery translates the mRNA into protein. In contrast, when SeV infects host cells, SeV genomic RNA (negative strand RNA) is transcribed into antigenomic RNA by the viral RNA-dependent RNA polymerase, the antigenomic RNA is used to replicate the genomic RNA, and copied genomic RNA is transcribed into mRNA, which is translated into protein. In view of these very different replication systems, one skilled in the art would have had no reasonable expectation of success for use of a negative-strand RNA virus expressing an immunodeficiency viral protein as a vaccine or a vector that can induce an immune response to the immunodeficiency viral protein, even if DNA viruses were known to be useful as gene-transfer vectors for vaccination, and negative-strand RNA viruses were known to be useful as expression vectors.

7. I draw the Office's attention to Exhibits A, B, and C to this declaration.

8. Exhibit A is a press release of the International AIDS Vaccine Initiative ("IAVI"), dated July 9, 2007, describing the collaboration between IAVI and DNAVEC, in developing a Sendai-virus ("SeV") vector-based human vaccine for AIDS as presently claimed.

9. Exhibit B is an article published in the Daily Yomiuri Online on July 8, 2007, further describing the collaboration between IAVI and DNAVEC in developing a human vaccine for AIDS as presently claimed.

10. Exhibit C is an English translation of an abstract of a DNAVEC press release, dated May 25, 2007, describing a contract between DNAVEC and Shenzhen SiBiono GeneTech Co., Ltd. ("SiBiono") executed on May 25, 2007 concerning the licensing of the AIDS vaccine technology as presently claimed to SiBiono. The original Japanese-language DNAVEC press release is also included in Exhibit C.

11. IAVI, the world's largest institution for AIDS study and prevention, has agreed to provide billions of yen of financial support to DNAVEC for the development of a human vaccine for AIDS. IAVI is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI is operational in 24 countries and is supported by the Bill & Melinda Gates Foundation, the Alfred P. Sloan Foundation, the Foundation for the National Institutes of Health, and many other organizations and national governments.

(See paragraphs 4, 5, and 10 of Exhibit A, and paragraphs 1 and 8 of Exhibit B.)

12. Most of the approximately 30 candidate AIDS vaccines in clinical trials are based on a cell-mediated approach, targeting only one arm of the human immune system, and none have been developed for practical use. The SeV vaccine candidate under development by DNAVEC is designed to be administered intranasally in order both to stimulate immune responses in the blood and to stimulate several types of immune cells via mucous membranes, the initial point of entry for HIV. (See paragraphs 1 and 2 of Exhibit A and paragraphs 3 and 5 of Exhibit B.)

13. SeV, a key component of DNAVEC's candidate, claimed vaccine, is an RNA virus that does not cause disease in humans, is capable of efficiently delivering genes expressing HIV proteins to the immune system, and can replicate safely in the upper airway. The vaccine does not adversely affect normal cells in the body, as the vaccine components do not impact human DNA. Furthermore, the vaccine has proved highly effective in animal experiments. In particular, DNAVEC has demonstrated that monkeys that have been vaccinated intranasally using a recombinant SeV vaccine candidate can be protected against SIV, a virus that causes a disease in some non-human primates that is similar to AIDS. Finally, the vaccine is expected to provide a longer protection period than other vaccines. (See paragraph 3 of Exhibit A and paragraphs 2, 5, and 9 of Exhibit B.)

14. In addition, DNAVEC has shown that the SeV vaccine not only prevents

AIDS-like infections but also slows the reproduction of the virus in monkeys that are already infected. (See paragraph 6 of Exhibit B.)

15. As Exhibits A, B, and C demonstrate, DNAVEC has achieved commercial success in attracting the partnership and substantial financial investment of IAVI, the world's largest institution for AIDS study and prevention, in connection with the claimed compositions and methods.

16. In addition, DNAVEC has received praise by others in developing an AIDS vaccine as presently claimed. The fact that IAVI has agreed to provide billions of yen of financial support to DNAVEC for the development of a human vaccine for AIDS as presently claimed constitutes significant praise. Seth Berkley, CEO and president of IAVI, has stated: "Japanese biotechnology companies such as DNAVEC, with a proven capability in developing innovative vaccine concepts, will play a large role in the global search for a vaccine to end AIDS." (See paragraph 8 of Exhibit A.)

17. Furthermore, DNAVEC has successfully licensed the presently-claimed SeV vaccine technology to SiBiono, a leading Chinese company. (See Exhibit C.)

18. The inventive contribution of applicants in the present application has led directly to a vaccine candidate that has many of the characteristics that have long been sought in an AIDS vaccine, as described above, and that has notable advantages over other vaccines currently in clinical trials.

19. All statements made herein of my own knowledge are true and all statements

made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Oct. 29, 2007
Date

Mamoru Hasegawa
Mamoru Hasegawa, Ph.D.

EXHIBIT A

Japan's DNAVEC and IAVI Partner on Novel AIDS Vaccine Strategy

09 July 2007

New class of viral vector tapped to target primary site of HIV replication; Agreement marks IAVI's first product development partnership with Japanese company

Tsukuba City, Japan and New York, July 9, 2007—The New York-based International AIDS Vaccine Initiative (IAVI) and DNAVEC Corporation today announced a collaboration to jointly develop an AIDS vaccine using DNAVEC's
1 Sendai virus (SeV) vector technology. The candidate will be designed to be administered intra-nasally to stimulate immune responses in both the blood and mucosal tissues, the initial point of entry for HIV.

This direction in AIDS vaccine development is crucial: Today, most candidates in clinical trials — numbering close to 30
2 — are based on a cell-mediated approach, targeting only one arm of the human immune system. Promising vectors that trigger mucosal immunity at the primary site of infection and replication could serve as a first line of defense in fending off the virus. These properties may be necessary for an efficacious vaccine.

Sendai, which serves as a basis of the vector, is a RNA virus that does not cause disease in humans, is capable of efficiently delivering genes expressing HIV proteins to the immune system, and of replicating safely in the upper airway.
3 DNAVEC and the Japanese National Institute for Infectious Diseases (NIID) have demonstrated that monkeys can be protected against SIV, a virus that causes a disease in some non-human primates that is much like AIDS, if vaccinated intra-nasally using a recombinant SeV vaccine candidate.

"One of IAVI's scientific priorities is to develop vaccines by using new and improved viral vectors that can control HIV infection," said Seth Berkley, CEO and President of IAVI. "The preliminary data from DNAVEC and the Japanese NIID
4 in monkeys makes SeV a promising candidate, and we are delighted to be working with our first Japanese industrial partner on the project." Since its inception in 1996, IAVI has tested six candidate vaccines and raised nearly a half billion dollars in new funding for AIDS vaccine research and development.

IAVI and DNAVEC will each contribute scientific and technical expertise to develop the SeV vector-based AIDS vaccine, with a goal of advancing the candidate to human clinical trials within the next three years. The agreement includes pre-
5 clinical testing for immunogenicity and safety, process development for manufacturing, and a Phase I clinical trial for the candidate. The partners will evaluate further development after the results of early testing. DNAVEC will receive royalties from any vaccine licensed for use in developed countries, while both partners have agreed to make any successful vaccine available as quickly as possible to countries hardest hit by the epidemic. IAVI also will provide financial support for the project.

"This agreement brings together IAVI's proven product development expertise and experience conducting clinical trials
6 in North America, Europe, Africa and India with DNAVEC's promising and unique vector technology," said Mamoru Hasegawa, President and CEO of DNAVEC. "We are very hopeful the partnership will bring us closer to a safe and effective AIDS vaccine, which would be a great contribution to human welfare."

Currently, there are close to 40 million people infected with HIV, most of them in developing countries, with the number of new infections worldwide topping 12,000 per day. Although the international community has made significant strides
7 in expanding AIDS treatment and care, HIV/AIDS is outpacing the global response. For every person who begins antiretroviral treatment for AIDS, estimates suggest six more become newly infected with HIV.

"We simply must do a better job of marshalling the scientific talent and resources from every corner of the globe to
8 design effective and long-term approaches to HIV prevention," concluded Berkley. "Japanese biotechnology companies such as DNAVEC, with a proven capability in developing innovative vaccine concepts, will play a large role in the global search for a vaccine to end AIDS."

To date, DNAVEC has worked with the University of Tokyo and the Beijing University of Technology to develop the
9 Sendai vector as a viable technology for HIV/AIDS vaccines.

About IAVI

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's
10 financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust, The Rockefeller Foundation, The Starr Foundation, The William and Flora Hewlett Foundation; the Governments of Canada, Denmark, Ireland, The Netherlands, Norway, Sweden, the United Kingdom,

and the United States, the Basque Autonomous Government as well as the European Union; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, Google Inc., Henry Schein, Inc., Merck & Co., Inc. and Pfizer Inc; leading AIDS charities such as Broadway Cares/Equity Fights AIDS and Until There's A Cure Foundation; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

About DNAVEC Corporation

DNAVEC Corporation is a venture company originally incubated as a Japanese national project supported by the Japanese Ministry of Health and Welfare. During its nine-year project period, DNAVEC Research Inc., the predecessor of DNAVEC Corporation, successfully developed innovative vectors including the Sendai virus vector system, which are expected to become an indispensable device for gene therapy. The company has obtained a number of international patents on these vectors and their use after initial testing predicted a high efficacy and safety profile. DNAVEC is currently promoting multiple joint research and development programs with national and global research institutes and pharmaceutical companies. Gene therapy research conducted by the Kyushu University Hospital for severe ischemic limbs using the Sendai virus vector received regulatory approval from the Ministry of Health and Welfare and was initiated in 2006. The Sendai virus vector is Japan' s first viral vector to be tapped for gene therapy. The vector bearing FGF-2, a therapeutic for severe ischemic limbs has been licensed to a major Chinese pharmaceutical company for use in China and is pending Chinese FDA (SFDA) approval. For more information, see www.dnavec-corp.com.

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Regional offices in Amsterdam, Delhi, Johannesburg and Nairobi

EXHIBIT B

DAILY YOMIURI ONLINE AP Associated Press News

JAPAN HOTELS ONLINE Confirmations Online! KINTETSU INTERNATIONAL EXPRESS

JAPANESE

Tsukuba firm working on vaccine for AIDS

The Yomiuri Shimbun

DNAVEC Corp., a venture firm based in Tsukuba, Ibaraki Prefecture, has begun developing a new AIDS vaccine in cooperation with the International AIDS Vaccine Initiative (IAVI), the world's largest institution for AIDS study and prevention, sources said Saturday.

The company's prototype vaccine has been highly effective in animal experiments. DNAVEC plans to improve the product to start clinical tests on humans in about three years.

Though medical institutions worldwide are working on a vaccine for AIDS, none have been developed for practical use. If DNAVEC starts clinical trials, its vaccine will be the first Japanese-made product to enter that stage. DNAVEC's predecessor was a company jointly established by an affiliated corporation of the Health, Labor and Welfare Ministry and pharmaceutical firms.

DNAVEC owns the patent for a technology that produces vaccines by inserting part of genes of disease-causing microbes into the Sendai virus, which was discovered in Japan.

DNAVEC's AIDS vaccine can be sprayed into the nose, stimulating several types of immune cells through the mucous membranes in the nasal passages. Another advantage of the vaccine is that it does not adversely affect normal cells in the body, as the vaccine components do not impact human DNA.

When DNAVEC and the National Institute of Infectious Diseases jointly tested the vaccine on monkeys, they discovered that the vaccine not only prevented AIDS infections, but also slowed the reproduction of the virus in monkeys that were already infected.

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IAVI, DNAVEC's partner in the project, is a New York-based institution that
7 receives major financial aid from donors that include Microsoft Corp. Chairman Bill Gates.

IAVI will provide billions of yen for development costs from the stages of
8 designing the vaccine to the application for government approval.

IAVI has conducted clinical tests of six types of AIDS vaccines in other
9 countries, including Thailand. But DNAVEC's vaccine is expected to provide a longer protection period than other vaccines, according to medical experts.

DNAVEC President Mamoru Hasegawa said the company plans to start clinical
10 trials in the United States and Africa in three years, aiming to put the vaccine into practical use eight years later.

(Jul. 8, 2007)

Science & Nature go

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AP News

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EXHIBIT C

Brief Abstract of the News Release about License Agreement
between DNAVEC and SinBiono

1 DNAVEC Corpotation (Tsukuba, Ibaraki, Japan) and Shenzhen SiBiono GeneTech Co., Ltd. (Shenzhen, China) concluded the contract on May 25, 2007.

2 The contract covers the items concerning licensing of the AIDS vaccine technology that used Sendai virus vector.

3 Sibiono has previously put the gene therapy medicine "今又生 (Gendicine) " for cancer on the market.

4 The Chinese Food and Drug Administration approved the sale of the above medicine in 2004.

5 The president of SiBiono is aiming at bringing the AIDS vaccine using the above technology into practical use in 4 or 5 years.

6 The AIDS vaccine that has been licensed-out to SiBiono is a Sendai virus vector containing a gene encoding Gag protein of human immunodeficiency virus (HIV).

7 The vaccine has the ability to induce cytotoxic T cells (CTL).

8 The expected effect of the vaccine is elimination of HIV infected cells by CTL, and inhibition of virus replication.

9 This vaccine was found effective in the "monkey acute AIDS model" using monkey-human chimeric HIV.

10 This vaccine was able to reduce the viral load below the detection limit in the "monkey chronic AIDS model " infected by SIV.

11 DNAVEC Corporation is carrying out a joint study on AIDS vaccine with Beijing Institute of Technology, and Chinese Center for Disease Control (CDC).

12 The representatives of the government of Henan Province as well as Chinese CDC and Beijing Institute of Technology were present at the signing ceremony of the contract by the two companies.

13 It is said that Henan Province is a region where the damage by AIDS is the largest in China.